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EXPERIMENTS WITH ALCOHOL AND WHITE RATS

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SINCE the familiar paper by Elderton and Pearson ('10) upon the physique and ability of children from alcoholic parents, much discussion has taken place on the relation of parental alcoholism to the condition of the offspring. A small proportion of this has been based upon experimental work with animals, as that of Stockard ('12 and '13), Stockard and Papanicolaou ('16 and '18), Nice ('12 and '13), Pearl ('17), and Arlitt ('19). From such studies there should be no hope of obtaining an immediate analysis of the human problem. In so far as alcoholism in man is sociological, involving factors of family life, environment and education, no study of laboratory animals can have significance. The way such studies may have a bearing upon the human problem is through the revelation of general biological reactions that may in all the animals available for study, be found so invariable that it becomes safe to conclude that they appear in man as well. How far the specific findings herein reported for white rats may apply to different animals is a matter for experiment and not conjecture. But even were such a biological analysis secured, the other phases of the human problem would not be solved.

From the data at hand are there any indications of general biological reactions that may have significance for all animals? Stockard and Papanicolaou, with guinea pigs, found that alcoholization of parents gave unfavorable results in the offspring; Pearl reported generally favorable results in the offspring of treated fowl; Arlitt reported unfavorable results from mild doses on rats, while Nice, also with mild doses, found his test mice slightly better in growth and fertility but less active, as measured by the revolutions of the revolving cages in which they were placed, than the controls. Earlier, Hodges ('03) had found the viability of puppies reduced by the treatment of their parents; the treated dogs were less active and more susceptible to distemper; Laitinen ('08) reported high rates of death at or soon after birth of guinea pigs and rabbits from treated parents.

Accepting these general statements as correct, there appears to be no obvious uniformity in the results obtained by different investigators. But this lack of uniformity may be only apparent; it is possible that not all the results as presented will be confirmed by subsequent investigations since none of the experiments reported have escaped unfavorable criticism from some standpoint. Alcoholism has such a multiplicity of aspects that it is a matter of great difficulty to arrange experiments concerning its effect on the offspring of treated animals that will be beyond criticism. For technique satisfactory to a physiologist may involve serious errors in the eyes of a psychologist, while the experiments of both may, to a geneticist, seem to have weak points. Until alcohol studies meet the requirements of all critics no final conclusions can be reached. In problems involving comparisons between experimental and control individuals the nature of the controls is no less important than the comparison itself. However true this appears to be for all experimental work, it is surprising to note that the main adverse criticisms of the experimental studies of the influence of alcohol upon the offspring have been aimed at the controls.

In spite of the general lack of uniformity in the results as they stand, at least one criterion appears to show consistency. This is the reproductive capacity of the treated individuals. All the experiments appear to indicate an immediate reduction in the number of offspring. The uniformity of this result tends certainly to increase its value as a *general* result; but even so, as long as the controls are subject to criticism, the apparent consistency may be due to the controls and not to the regularity of the reactions to alcohol. For a single result can not at the same time prove the reliability of the controls and the results of alcohol treatment. It is hoped that the controls employed in the following experiments will be found to approach the ideal of satisfying all requirements.

METHODS

In 1914 an investigation was undertaken upon the influence of alcohol on the untreated descendants of white rats with the primary object of studying the behavior, or learning capacity, in different generations. In the summer of 1917 war conditions necessitated repeated reductions of the stocks until, by the end of the next year, the material was completely lost. This calamitous termination of the work must be borne in mind, for, in spite of the final nature of this report, the data come from an investigation that was not completed.

Material and Breeding.—The rats employed belonged to four strains; three of these strains originated respectively from three pairs of rats in the Wistar Standard Stock, the fourth strain had been bred in this laboratory for three generations. All matings were between full brothers and sisters. When 28 days old the litters used to start these experiments were divided into two lots on the basis of equal weight and equal numbers of each sex; one of these lots was used as controls, the other was treated. All matings were between the original treated males and females or their descendants, or between the original control males and females or their descendants. In each generation the control matings parallel those of the descendants of the treated animals, so that each group of test animals in each generation had its own particular group of controls. Since inbreeding was the rule, the closest possible relationship for the tests and controls in the successive generations was secured; they came from a single pair of grandparents or great-grandparents, and were thus raised at the same time, and after the same number of generations of inbreeding.

Treatment.—The treatment of these rats was by means of the inhalation method, now made familiar by the work of Stockard and Pearl. The rats were placed in closed tanks filled with alcohol vapor; these tanks have been described in detail elsewhere (MacDowell and Vicari, '21). Beginning at weaning (28 days) the rats to be treated were placed in the tanks for 30 minutes a day for 7 days. After this the duration of the daily treatment was measured by the reactions of the animals; for the next 14 days the rats were left daily in the fumes until they were obviously under their influence; subsequently the rats were left each day until they were completely anesthetized. This required from three to four hours for the older rats.

Criteria.—The term *treated* is used to indicate rats that were placed in the alcohol fumes after birth. The following generations are herein reported: (1) the treated rats, (2) the treated offspring, (3) the untreated offspring, (4) the untreated offspring of (3) (second untreated generation following one treated generation). For these rats the following types of data are given: the behavior in the maze, as measured by time per trial; behavior in a multiple choice apparatus, measured by the number of correct first choices; fertility, judged by the size of the litters and the number of litters; body weight, as judged by growth curves based on weekly weighings.

MAZE-BEHAVIOR

Apparatus and Training.—The maze used in this study was built according to the details given by Watson ('14); namely, a concentric arrangement of five alleys with doorways and blind alleys so arranged that the true path from the outside to the center required a rat to turn alternately to the left and the right at successive doorways. A rat's training was started at the age of 56 days, after preliminary feeding in the center of the maze on each of the 7 preceding days. Three successive trials a day were given. After the first and second trials the rat was removed from the center as soon as it had tasted the food (bread and milk) which was always found there; after the third trial, it was allowed to eat for five minutes. This training was given for eight successive days. The observations were so automatic that there was practically no possibility that the results were being influenced by an unconscious bias on the part of the observer. In the case of the treated rats the alcohol was given each day following the trials in the maze.

Results.—The average time per trial for each day of the training of the different groups of rats is represented in Fig. 1. The test rats, whether actually treated, or the descendants of treated rats, are represented by the broken lines, and their respective controls by the solid lines. The numbers of rats included in the different curves, beginning at the left, are as follows: 55 treated rats and 62 controls; 46 tests and 48 controls; 25 tests and 25 controls; 8 tests and 20 controls. The broken lines tend to lie above the solid lines. The tests tend to give higher time averages than the controls, that is, the tests took longer time to run a trial. The inferiority shown by the treated offspring from treated parents (fourth pair of curves), and by the untreated offspring from untreated parents and treated grandparents (third pair of curves) is of the same order of magnitude as that shown by the treated animals themselves; untreated offspring from treated parents show less inferiority than their own untreated offspring. Considering the significance of the differences between the tests and controls for each day independently, the following results are found: the differences between the tests and controls are over three times their probable errors on five days in the first pair of curves, on no day in the second pair, on four days in the third pair and one day in the fourth pair. All the significant differences favor the controls. However, more important than the significance of individual differences as measured by the probable errors, is the agreement in the direction of the differences on successive days. The fact that the differences on eight successive days lie in the same direction probably has more significance than that half of these taken separately may be significant as judged by their probable errors. Considering the signs alone, in all the curves there are three out of the 32 points of comparison showing the test averages lower than the controls. One of these cases is on the third day of training of the untreated rats from treated parents, the other two cases are on the second and third days of training of the treated rats from treated parents. If chance alone is working, the probability of

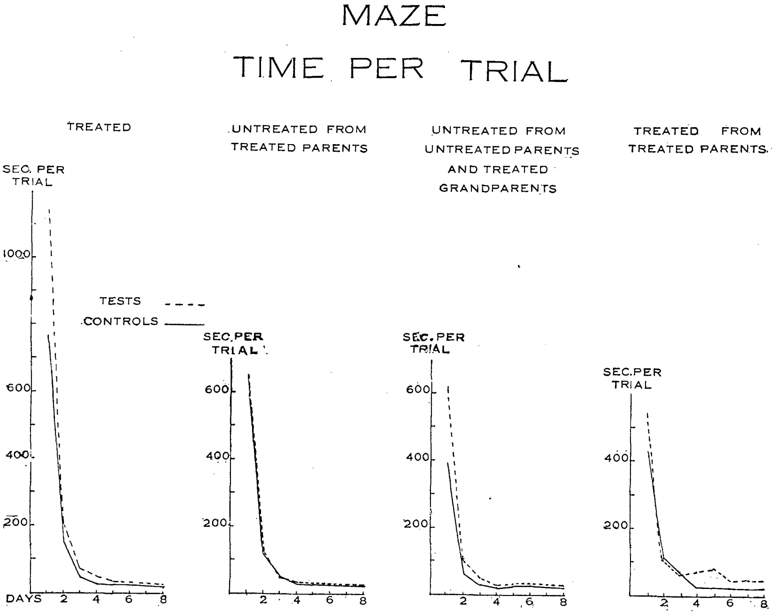


Fig. 1. Comparisons of time averages in four groups of rats—those treated, their treated and untreated children, and their untreated grandchildren. (Data for the third set of curves taken from MacDowell and Vicari, '21, p. 233.) Broken lines tests, solid lines controls.

eight days giving differences in the same direction is the same as the probability of eight coins coming down all heads; in the long run this will happen once in 256 tosses. The chances of seven out of eight, 1 to 32, of six heads out of eight, 1 to 9. Carrying this comparison further by considering all the generations together, the chances of finding three cases favoring the tests out of thirty-two are in the neighborhood of 1 to 860,000. From all this it appears that the test rats are different, as a group, from the controls. Apparently the only difference between the tests and controls that could explain this result is the alcohol treatment given directly, or in the ancestry of the test rats; this leads to the conclusion that the difference in behavior is due to the alcohol treatment.

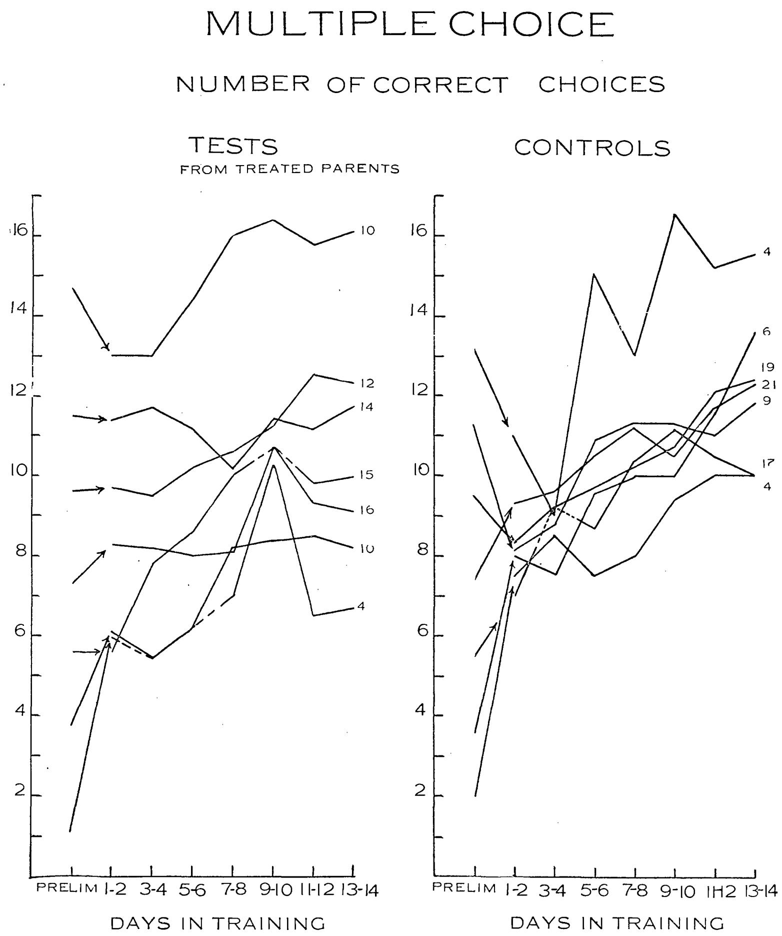
BEHAVIOR IN THE MULTIPLE CHOICE APPARATUS

The difference in the behavior of the tests and controls in the generation of the untreated offspring of treated parents is further shown by the training on the multiple choice apparatus. This is the only generation from which sufficient data were gathered for the analysis of behavior on this apparatus.

Apparatus and Training.—The apparatus used in this training consisted of a linear series of nine compartments, with front and back doors operated at a distance by the observer (see Yerkes, '21, for history and uses of this apparatus). Different sets of front doors were opened for the successive trials and the rat was given its reward of food by raising the back door when it entered the "correct" compartment. The "correct" compartment was the one at the extreme right or left (according to the problem) of the series with open front doors. In successive trials, therefore, the correct compartment was never the same one, and the solution of the problem did not depend upon the repetition of a regular kinesthetic habit. The steps in the training were these: at the age of 65 days the preliminary training was started; on the first two days the doors were all left open and food was exposed to view in every compartment; the rats in groups of five or so were left to run at random in the apparatus. On the second two days the front doors were all open as before, but the food was concealed by covers fastened to the back doors, and when a rat entered any compartment the food was revealed by opening the back door; the rats were run singly on these two days and given ten such feedings a day. On the last two days of the preliminary training only the regular series of doors were opened, but the rats were fed on entering any compartment (20 trials).

Right-hand Problem.—In the first problem the rat was fed only when it entered the right-hand compartment of any set-up (those open in any trial); after wrong choices the rat was confined in the compartment for half a minute, and then, by raising the front door, was permitted to make further choices (10 days, 100 trials); next, the same problem was given with a different series of open doors (2 days, 20 trials). Further training was given in the form of a problem in which the correct door was the open one at the left end of the open series, but the results from this problem are so complicated that they will not be treated at this time. The main reason for this complication is the fact that at the end of the time allotted for the mastery of the first problem the test and control rats exhibited different degrees of perfection; some had made considerable progress in learning, while others had made very little advance. Accordingly, when the reverse problem was given, those that had learned the most were handicapped by the habit already acquired, while those that had not formed the required habit in the first problem were able to progress more rapidly in learning the second problem.

Results.—From a study of the individual reaction tendencies as revealed in the last two days of the preliminary training before the problem was presented, and in the regular training after the presentation of the problem necessitated the use of the trial and error method of finding the correct compartment, it appeared that the test rats continued the same tendencies in the regular training that were initiated in the preliminary training, but the controls, on the other hand, modified their reaction tendencies as soon as the regular training was started. This result is brought out by the curves in Fig.


MULTIPLE CHOICE

NUMBER OF CORRECT CHOICES

TESTS
FROM TREATED PARENTS

CONTROLS

FIG. 2. Showing the relationship for rats from treated parents between preliminary and subsequent performance in the multiple choice apparatus. Average numbers of correct first choices are shown for each successive set of 20 trials. The rats have been classified into groups according to their preliminary records. The figure shows that the behavior of the tests in the preliminary trials is a fairly good index of their behavior in the regular training, but the behavior of the controls in the preliminary trials gives very little indication of the later behavior.

2. The test rats have been classified into seven groups according to the number of right-end choices in the last twenty trials of their preliminary training. The first points of the lines given for the tests indicate the average number of right-end choices made by the rats in each of the groups in the preliminary training; the following points give the average numbers of correct (right-end) choices made by these same rats in successive sets of 20 trials in the regular training. Since the procedure in the regular training is essentially different from that in the preliminary trials, the lines connecting the first and second points are drawn as arrows. The numbers at the ends of the lines give the numbers of individuals included in each group. The arrangement of the controls follows the same plan. Whereas the curves for the tests show a general parallelism, those for the controls are, with the exception of the group of four rats whose preliminary training gave between 12 and 14 right-end choices, relatively independent of the preliminary records. This matter can be brought out more clearly by a study of the coefficients of correlation between the preliminary record of each rat and the trials in the regular training. When the correlation coefficients between the preliminary records and the first 20 trials in regular training, and between the preliminary and the second twenty trials in regular training, etc., are calculated, the figures in Table I are obtained. In every case the differences between the coefficients of the tests and controls (fourth column in Table I) show that the tests have higher correlations, and in all but the correlation between the preliminary trials and the last set of twenty trials in regular training, the differences are statistically significant. These results indicate that there is a real difference between the tests and controls in the way they react to the necessity of using trial and error methods; this may be due to a difference in responsiveness to changes in the situation. The tests appear to be less responsive to the changed procedure, since they continue the same general behavior

as in the preliminary training, whereas the controls modify their behavior as soon as the change is made in the procedure.

TABLE I

CORRELATION COEFFICIENTS, SHOWING THE DEGREES OF SIMILARITY BETWEEN THE NUMBER OF RIGHT-END CHOICES IN THE LAST 20 TRIALS OF THE PRELIMINARY TRAINING AND THE CORRECT CHOICES IN EACH SUCCESSIVE SET OF 20 TRIALS IN THE SUBSEQUENT TRAINING IN THE MULTIPLE CHOICE APPARATUS.

Trials Correlated	Correlation Coefficients		Difference	*D*/P.E.
	Tests	Controls		
Preliminary by 1st 20 trials....	.688±.039	.139±.063	+.549±.074	7.4
by 2d " "	.628±.045	.072±.075	+.556±.087	6.3
by 3d " "	.592±.048	.339±.067	+.253±.082	3.1
by 4th " "	.444±.060	.070±.075	+.374±.096	3.8
by 5th " "	.432±.061	.101±.074	+.331±.095	3.4
by 6th " "	.489±.057	.049±.075	+.440±.094	4.6
by 7th " "	.342±.061	.212±.072	+.220±.094	2.3

All the coefficients are positive; the plus sign is used before the differences to indicate that the coefficients for the tests are higher than the corresponding ones for the controls.

In view of the above, the direct comparison of the averages of the tests and controls in regular training would lead to error unless the average performance in the preliminary training happened to be the same for both sets. In the long run this would undoubtedly be the case, but, as it happens, the averages for the tests and controls do not agree in the preliminary training. However, it was found that this difference depended upon the rats with strong right- or left-hand tendencies, for if these (those tests and controls with more than 12 or less than 3 right-end choices in the preliminary training) be omitted, the average of all the rest of the rats was the same for the tests and controls. Using the rats whose preliminary records showed between 3 and 12 inclusive right-end choices, the averages for the curves in Fig. 3 were obtained. Starting with the same average tendency to enter the right-end compartment in the preliminary training, the controls increase the number of correct first choices more rapidly than do the tests, and as the difference between the averages increases it becomes statistically significant.

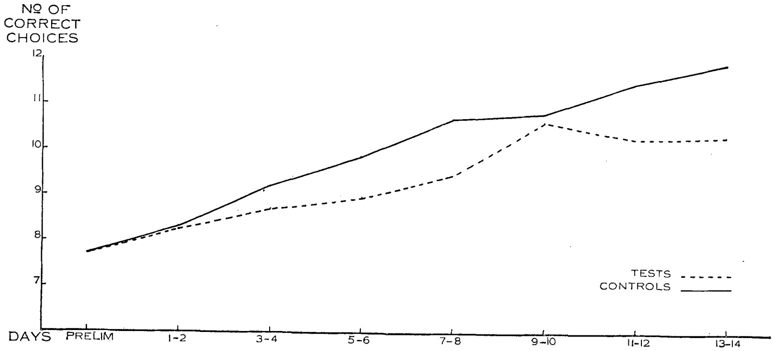


FIG. 3. Average numbers of correct first choices in the multiple choice apparatus, in the preliminary training and in the following pairs of days, when only those rats are included which made from 3–12 correct first choices in their preliminary training, *i.e.*, *eliminating* rats with strong tendencies either to choose or avoid the correct door, before regular training began. In this way the preliminary averages of the tests and controls are brought together and it becomes possible to compare the averages in the regular training.

Granting that the controls are adequate, the data on behavior indicate that a modification has been brought about by the alcohol; the generation showing the least absolute difference in maze-behavior is shown to be definitely modified when the tests are made on a multiple-choice apparatus.

Fertility

Compared with the difficulty of measuring the behavior tendencies of rats, the measure of fertility is very simple and definite. However, the great amount of time required by the behavior studies prevented the collection of many of the available data on the purely physiological side. As a result of this, instead of the long list of criteria of fertility that have been given by other authors, it is possible to give only two with any degree of accuracy and completeness. These are: the number of rats in a litter, and the number of litters. A more detailed report on the data leading to the following conclusions may be found elsewhere (MacDowell, '22*a*).

Size of Litters.—A general tendency for the litters of the test rats to be smaller than the controls persists in the summaries of all generations. The difference between the size of the litters from the original treated rats and the litters from the controls is equal to 10.5 per cent. of the size of the control litters. The treated offspring of the treated rats produced litters that were 10.3 per cent. smaller than the litters of their controls. It appears, therefore, that the treatment of the parents of the litters as well as the grandparents does not intensify the reduction in litter size found when only one generation was treated. The untreated offspring from treated rats gave litters that were 11.2 per cent. smaller than their controls, and the untreated offspring from untreated parents and treated grandparents gave litters that were 13.1 per cent. smaller than the controls (see Fig. 4). These differences in individual generations are based on too few cases to be significant when compared with their probable errors, but when the numbers are increased by taking all the generations together, the probable error is reduced so that the difference attains statistical significance (3.6 times its probable error). Litter size, then, gives a result not unlike that given by the behavior data: the tests are inferior in each generation, with no apparent relation to the proximity of the alcohol or the number of generations of treatment.

Number of Litters.—Given equal time, the treated pairs produced 0.72 litter per pair while the controls produced 2.07 litters per pair. This is a reduction of 64.8 ± 3.3 per cent. in the number of litters, and as it is 19.2 times its probable error, it is significant beyond all question. The test litters were slower in appearing than the controls. The treated rats from treated parents also gave fewer litters than their controls, but instead of a greater reduction than in the previous generation this second treated generation produced relatively more litters. The reduction was 35.4 ± 6.9 per cent. of the controls. Coming to the rats not directly treated, the untreated rats

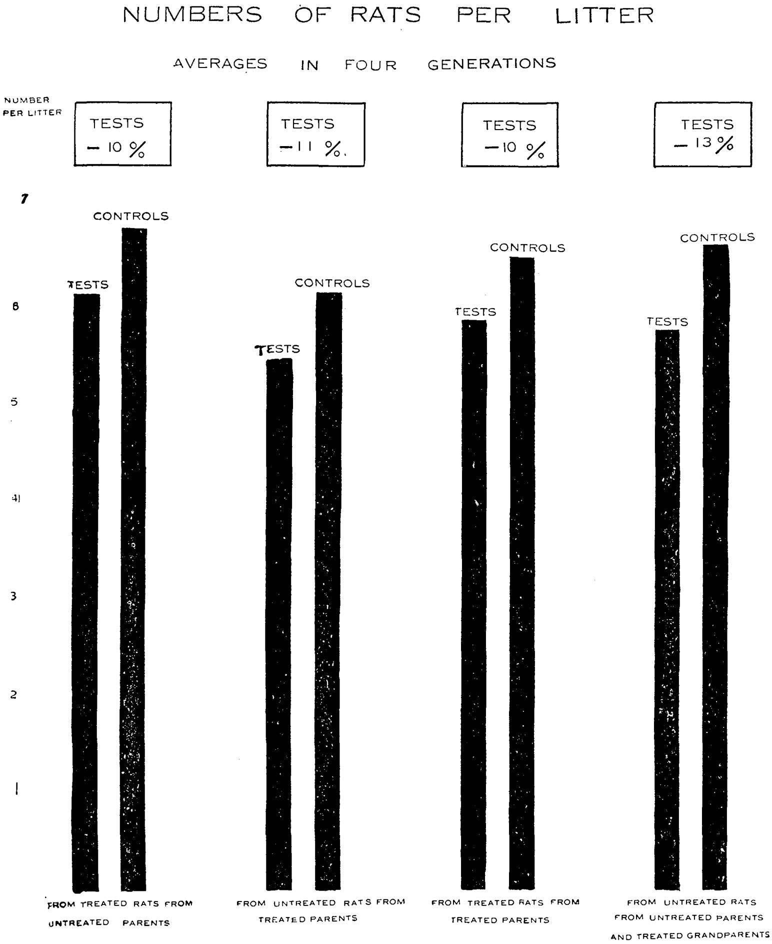


FIG. 4. Average litter size for the controls and tests bearing the relationships to the alcohol treatment indicated.

from treated parents gave 33.3 ± 8.2 per cent. *more* litters than their controls, and the untreated rats from untreated parents and treated grandparents produced 55.6 ± 8.4 per cent. *more* litters than their controls (see Fig. 5). All of these differences are, without doubt, statistically significant.

Discussion.—Two generations of treatment made less difference in number of litters than a single generation of treatment, and two untreated generations following

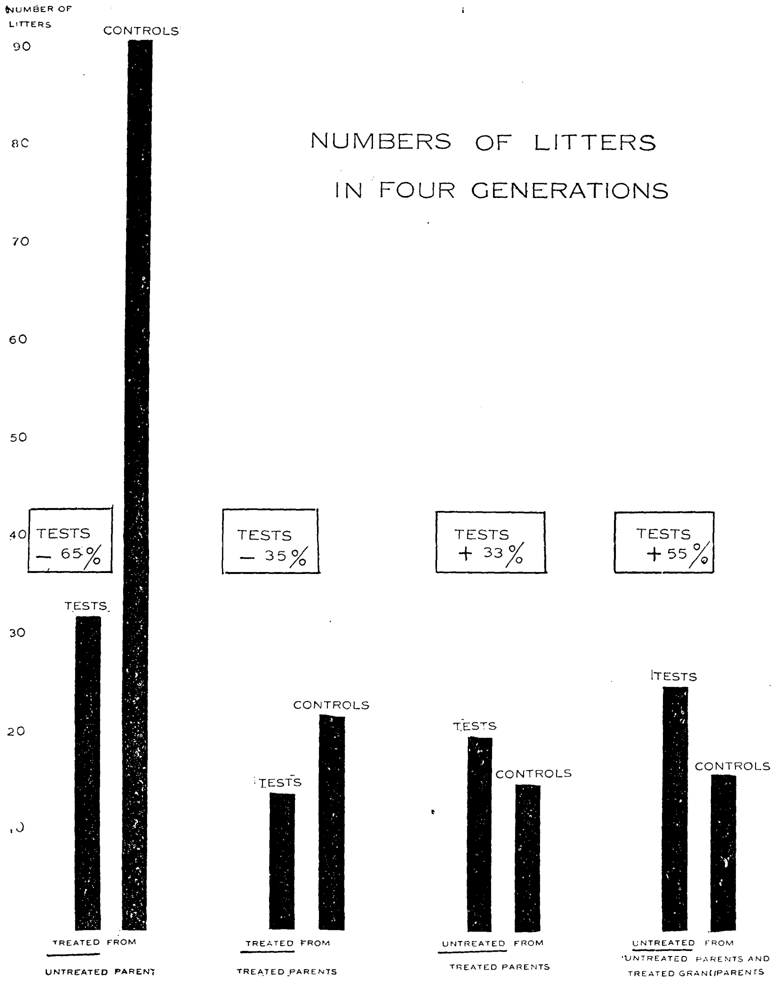


FIG. 5. Relative numbers of litters produced in equal periods by the test and control rats in different generations. Beginning at the left the test litters were produced by the following numbers of pairs: 44, 9, 10, 11; in each case the control litters have been given on the basis of equal numbers of pairs, although the actual numbers of control pairs involved were: 42, 12, 10, 13.

the treatment produced more litters than the controls. The number of litters is strongly reduced when the parents themselves are treated, but when the alcohol is more remote, the reduction vanishes and the untreated descendants of the treated rats produce *more* litters than their controls. To explain the reduction in the number of litters in the presence of alcohol along purely physiological lines would be a simple matter, but a genetic explanation appears to be required when it comes to the increase over the controls given by untreated descendants of treated animals. No general depression or stimulation will account for the continuation of small litters together with the increase in number of litters in the generations not given alcohol directly. It seems necessary to assume that there are genetic factors influencing the number of litters; alcohol prevents the reproduction of such females as carry factors working in the direction of lower reproductive capacity, so that the litters come alone from females carrying higher litter-producing capacity; the next generation will produce higher numbers of litters than the unselected controls, for the controls still carry all grades of fertility, while the tests lack the genetically lower grades. The treated offspring of treated rats produced fewer litters than their controls, but genetically they were superior, as shown by untreated offspring giving more litters than their controls; they were superior to the first generation, for, instead of a 65 per cent. reduction, they gave only a 35 per cent. reduction in the number of their litters. Whereas the immediate presence of alcohol reduces the number of litters, it acts to increase the number in the next generation; therefore alcohol may produce two results upon a single character in two generations. This could lead to much confusion were it not so easy to understand the first result as the cause of the second.

This selective action of alcohol will account for the results from the number of litters, but will not account for the uniform results given by litter size. If this is a correct statement of the situation, it indicates that the number of litters is influenced by genetic factors that are not identical with those influencing litter size. Although such a distinction between genetic bases for the numbers of litters and litter size has apparently not been made, it is not difficult to conceive, for litter size is largely dependent upon the number and constitution of the germ cells liberated, while the somatic condition of the mother plays a part in determining whether or not a litter will be produced. The results from litter size agree strikingly, qualitatively and even quantitatively with those of Stockard and Papanicolaou from similar studies with guinea pigs; the results from the number of litters agree with Pearl's on fowl in so far as they may be interpreted by assuming a selective action of the alcohol working upon existing genetic differences. In the fowl the alcohol appears to select between germ cells; in the rats it appears to select between mothers of different physiological and genetic grades.

WEIGHT

The data on weight (see MacDowell, '22*b*) form an extensive series consisting of weekly weighings of practically all the rats raised in the various generations herein described. Individual growth curves were plotted and from these the weights at six ages were taken for statistical study. This procedure was necessitated by the fact that all the rats were weighed on the same day each week, so that the rats were of different ages. The results are based primarily upon the males (see Table II), since the pregnancies of the females make their data less reliable. However, when the data from the females with arbitrary smoothing of the pregnancy peaks are summarized, the results so obtained support those given by the males. Each of the four strains shows that the treated rats grew more slowly than the controls. This is an influence shown by the population as a whole, although there are some individual treated males that remained as heavy as the heaviest controls. The untreated offspring of the treated rats tended to grow more rapidly than their controls. This result is not so clear as the opposite result in the preceding generation; the absolute differences are not so large and the strains do not show this in equal measure. Treated rats from treated parents barely differ at all from their controls. Very little can be concluded from the weights of the untreated offspring from untreated

TABLE II

THE WEIGHTS AT SUCCESSIVE AGES OF THE VARIOUS TYPES OF MALE TEST RATS COMPARED WITH THEIR RESPECTIVE CONTROLS.

Relation to Alcohol Treatment	Age in Days	Tests		Controls		Difference	*D*/P.E.
		Grams Averages	Nos.	Grams Averages	Nos.		
Treated from normal parents	40	70.43	70	72.95	64	+ 2.52 ± 1.40	1.8
	60	116.66	71	129.35	65	+12.69 ± 2.16	5.9
	90	149.63	61	176.63	55	+27.00 ± 3.16	8.5
	120	192.10	50	229.71	46	+37.61 ± 4.07	9.2
	150	215.39	38	257.97	39	+42.58 ± 4.81	8.8
	180	235.88	34	274.34	32	+38.46 ± 5.11	7.5
Treated from treated parents	40	83.86	15	81.81	16	− 2.05 ± 2.73	0.7
	60	128.00	15	131.81	16	+ 3.81 ± 3.81	1.0
	90	166.50	14	166.37	16	− 0.13 ± 4.96	0.0
	120	198.07	14	207.50	14	+ 9.43 ± 6.01	1.5
	150	228.33	12	236.50	14	+ 8.17 ± 6.48	1.2
	180	245.70	10	258.00	13	+12.30 ± 7.44	1.6
Untreated from treated parents	40	73.03	26	63.82	29	− 9.21 ± 2.37	3.8
	60	95.53	26	84.13	29	−11.40 ± 2.56	4.4
	90	127.26	26	117.79	29	− 9.47 ± 3.64	2.6
	120	195.26	26	182.14	27	−13.12 ± 5.13	2.5
	150	230.42	26	219.88	27	−10.54 ± 6.24	1.6
	180	249.00	25	238.85	27	−10.15 ± 7.61	1.3
Untreated from untreated parents and treated grandparents	40	75.90	10	80.57	7	+ 4.67 ± 5.08	0.9
	60	111.18	11	97.20	10	−13.98 ± 5.36	2.6
	90	131.54	11	125.90	10	− 5.64 ± 11.64	0.5
	120	191.63	11	171.30	10	−20.33 ± 16.66	1.2
	150	226.09	11	208.00	10	−18.09 ± 16.20	1.1
	180	235.54	11	230.20	10	− 5.34 ± 13.52	0.4

Plus signs indicate the controls heavier; *D*/PE.—difference divided by its probable error.

parents and treated grandparents. Two of the three strains represented in this generation show heavier averages for the tests and the third shows heavier averages for the controls; when all the strains together are considered (as in Table II), the test averages are higher at all ages.

This shows a marked similarity to the results from the number of litters; just as the offspring of the treated rats appear to be genetically superior to the controls in the matter of litter production, so they are found to be superior in the matter of weight, with the result that when they themselves are treated, the immediate reducing effect of the alcohol makes them about equal somatically to their controls, instead of growing markedly slower as did their parents. This likeness in results leads to a similar interpretation for the weight as for the number of litters: the alcohol has acted as a selective agent, eliminating germinal material that included factors for slower growth.

Discussion

In view of the premature termination of these experiments no discussion or interpretation can be justified other than by its possible influence upon future work.

The data on behavior and litter size taken alone may, if the controls are accepted as adequate, be considered to lead to the general interpretation of a direct and definite modification of the germinal material brought about by the alcohol treatment. On the other hand, the data on the number of litters and weight, when taken alone, agree in inviting the interpretation that the alcohol has acted as a selective agent upon germinal differences that were present in the germinal material of the original animals. One tendency pulls the race down, the other, by sacrificing the fullest reproductive expression of the treated individuals, tends to pull it up. The specific conditions found then are end-results that depend upon the interaction of different influences and do not measure directly the amount of influence exerted by the chemical.

Obviously, the situation is complicated, and equally obvious is the impossibility of proving the individual effects of two or more influences acting simultaneously. However, in this case the evidence favoring one supposition (that of selective elimination of germinal material) is very much more convincing than that favoring the supposition of germinal modification. So great, indeed, is this difference that the evidence of direct modification could easily be brushed aside and selective elimination be effectively championed as *the* effect of the alcohol, although even this involves two opposite results depending upon the proximity of the alcohol. But if a true statement of the situation is desired, the conflicting evidence must not be brushed aside.

If the germinal variability existing in the race is greater than the variability caused by the direct action of the alcohol upon the germinal material, the results actually obtained would be expected; that is, the effects of selective elimination would appear more striking in the end results. Since the reductions in litter size and in behavior stand in spite of an apparently much stronger racial improvement, these reductions give stronger support to the supposition that germinal modification is a second activity of the alcohol than is indicated by their magnitude.

The fact that so many different conclusions have been reached by different investigators from experiments with alcohol would in itself suggest very strongly that the action of this chemical upon animals is not simple and direct like the action of an acid upon a base, yet the general attitude toward the problem seems to have been that there should be a single answer, in one direction or the other, and that as soon as an investigator devises the perfect method, this answer will be disclosed. As long as such an attitude persists the alcohol problem will flounder about in the morass of futile and inconclusive papers. The moment chemistry, and later, experimental breeding, turned away from end results to the phenomena behind them (elements or factors), new epochs were started in these sciences. The problem should not be to judge how bad are the results of alcohol, but rather to find through what channels alcohol may work. The final results will differ in different cases according to differently combined influences of various sorts, just as the same combination of chemicals will yield different results under different conditions, and the same combination of genetic factors will yield various somatic expressions; to know the *modus operandi* of alcohol is fundamental.

CONCLUSIONS

1. Beginning at the time of weaning, alcohol was administered to white rats every day, in sufficient quantities to cause complete anesthetization. This treatment appears to account for the following differences between the treated rats and their normal sibs:

The treated rats—(*a*) took more time running the maze.
(*b*) produced smaller litters.
(*c*) produced fewer litters.
(*d*) grew more slowly.

2. The treated offspring from the treated rats differed from their controls in the following ways:

The treated offspring—(*a*) tended to take more time in running the maze.
(*b*) produced smaller litters.
(*c*) produced somewhat fewer litters.
(*d*) grew at a very slightly lower rate.

3. The untreated offspring from the treated rats differed from their controls in the following ways:

The untreated offspring—(*a*) took a very little longer in running the maze.
(*b*) produced smaller litters.
(*c*) produced more litters.
(*d*) were heavier.

4. The untreated offspring in the second generation from alcohol treatment differed from their controls in the following ways:

The second generation of untreated offspring—

(*a*) took more time in running the maze.
(*b*) produced smaller litters.
(*c*) produced more litters.
(*d*) were somewhat heavier.

5. From these results it is concluded that the action of alcohol is complicated; that it works in two or more different ways. The data on behavior and litter size suggest that the alcohol may modify germinal material directly. The data on the number of litters and growth indicate that the direct effect of alcohol upon these characters is in one direction and that its indirect effect is in the opposite direction; this may be interpreted by the assumption of a selective rôle played by the alcohol. It is urged that the alcohol problem can be settled biologically only when, instead of generalizing from the quality of specific end results, we deal with the channels through which alcohol may work.

Cold Spring Harbor,
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